[Artículos cientificos recientes de Ioannidis]:

COVID-19 Antibody Seroprevalence in Santa Clara County, California

Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters

What Other Countries Can Learn From Italy During the COVID-19 Pandemic

JOHN KIRBY: Dr. Ioannidis, when we spoke to you on March 23, you said we needed more data before we could ascertain what was happening. Since then, you've been busily gathering that data and have published three studies. Let's start with the latest one, which you entitle, "COVID-19, Antibody Seroprevalence in Santa Clara County, California." What was the purpose of that study, and what did you discover?

DR. IOANNIDIS: This study aimed to generate an estimate of how many people in Santa Clara County have been infected with the virus. And the way to find out is to try to see whether they have developed antibodies to SARS-CoV-2. So, we had a sample of residents in Santa Clara County evaluated for the presence of antibodies. And the sample was 3,300 people who came to be tested. We estimated that based on what we saw, between 2.5 and 4.2% of the population of the county has antibodies, which is an indication that they have been infected with the virus a while ago.

JK: What are your conclusions, based on your study?

DI: If you compare the numbers that we estimate to have been infected, which vary from 48,000-81,000, versus the number of documented cases that would correspond to the same time horizon around April 1st, when we had 956 cases documented in Santa Clara County, we realize that the number of infected people is somewhere between 50 and 85 times more compared to what we thought, compared to what had been documented. Immediately, that means that the infection fatality rate, the chance of dying, the probability of dying, if you are infected, diminishes by 50-85 fold, because the denominator in the calculation becomes 50-85 fold bigger. If you take these numbers into account, they suggest that the infection fatality rate for this new coronavirus is likely to be in the same ballpark as seasonal influenza.

Of course, there is still a little bit of uncertainty about the exact number, but it’s clearly very different compared to the original thoughts or speculations or preliminary data that suggested a much, much higher infection fatality rate.

JK: Could you imagine any way to ascertain the deaths that will be caused by this lockdown in deaths of despair, suicide, the after-effects from loss of work? Is there even an epidemiological way to count the devastation that has been wrought by the lockdown?

DI: I think that the devastation can be extreme, and it can be far worse than anything that coronavirus can do. I have to qualify that statement with the fact that we have never seen that before. So, we have to extrapolate from previous economic crisis and economic meltdowns that were nevertheless different. We've never seen such an acute meltdown. We've never seen such a set of perfect storm circumstances. In some ways, it could mean, also, that maybe we could be a bit more optimistic. For example, if this thing goes away, for one reason or another - let's say seasonality or suddenly the virus disappears, of course, that's a very optimistic scenario, and then everybody just forgets about it and just goes back to work, and just does whatever they used to do, one might argue that the damage will not be that severe. However, as you realize, this is not a scenario that is so easy to imagine.

Even if all the data tend to be optimistic, even if the cases start going down, the entire society has gone through a state of shock. It's very difficult to convince people to start doing again what they used to do. They will have a fear, justifiably so. They will avoid lots of things, and it will take some time to get back to normalcy, even if the virus kind of "disappears." There are data from previous economic crises that can give us some hint about the magnitude of the impact. For example, we

know that suicides go up by 1% for each 1% increase in unemployment, and as you know, as of now, we are talking about 25 million people filing for unemployment in this country, and probably almost 10 times that many around the world, becoming unemployed. And the number is rapidly increasing as we speak. We know that there's huge problems with other problems of common diseases, like cancer and heart attacks. They can go up, or actually, the trajectories of decrease that we have seen for many of these conditions are reversed, and they're not decreasing at the same slope, or actually even increase in situations of meltdown. Less people will die because of car accidents, but is that really a benefit to be proud of? And then there's other problems. There's all that meltdown of mental health. There's child abuse. There's domestic violence. We already see hints that these problems are escalating. Violence in general - we see that gun sales are escalating, and I do really worry about people who are locked down and desperate and losing their jobs and just feeling completely lost in a world that they cannot understand how it is evolving and why.

It's very, very difficult to fathom the consequences of what is going on and what we are doing, but I really worry that unless we manage to have a viable plan to exit from lockdown and shelter in place and reopen our world, the consequences will be far worse than coronavirus. Our data suggests that COVID-19 has an infection fatality rate that is in the same ballpark as seasonal influenza. It suggests that even though this is a very serious problem, we should not fear. It suggests that we have solid ground to have optimism about the possibility of eventually reopening our society and gaining back our lives.

JK: Sooner, rather than later, I hope?

DI: Sooner, rather than later with full control and a data-driven approach.

JK: I believe it's your most recent study talks about nosocomial infection. Could you tell us what that is and how it could be avoided?

DI: Nosocomial infection is infection that happens in the hospital. It's probably one mechanism that has contributed to the substantial number of deaths with coronavirus, with COVID-19, that we have seen in some epicenters of the pandemic, like some cities in Italy, some cities in Spain, and several locations in the US, prominently New York City and the New York metropolitan area. If you think that COVID-19 has pretty much the same infection fatality rate as, let's say, seasonal influenza, one immediately would argue, "Well, do we really see this type of disaster as we have seen in these particular cities with seasonal influenza?" And the answer is that, even with seasonal influenza, we do see, occasionally, some excess in specific locations. It's not that all locations are evenly hit. We do see hospitals crash occasionally, especially hospitals that tend to run close to full capacity, and have high numbers of susceptible populations like elderly, like in the case of Italy, or disadvantaged populations, like in the case of Queens, or other locations in New York City.

We do see that. But we don't really see that extreme concentration that we have seen with COVID-19. If you take the US data as of now, more than 50% of US deaths have accumulated in a very narrow strip of the country, New York City, Long Island, and New Jersey have the lion’s share of deaths. And If you look at Italy, the same thing: three cities, three regions, which don't really have a large population, account for about a quarter of all the deaths that were documented there. The common mechanism seems to be that in all of these locations, we had massive disasters, because we don't have a vaccine for coronavirus, in contrast to influenza, where medical personnel can be vaccinated, and therefore we don't get to see that much nosocomial influenza, influenza spreading within the hospital. For coronavirus, we don't have a vaccine. So, hospitals that are very close to capacity, like Queens for example, that tends to be a war zone even in summertime. If you get a very large number of people who come to the hospital with symptoms, they show up at the emergency room, they wait to be seen, probably, they start infecting each other, they can infect physicians, they can infect the nurses, they can infect personnel. Medical personnel, then, would infect other patients within the hospital, and the hospitals, typically, are the places where you find the most vulnerable people. You see elderly people, you see people with underlying diseases, you see people who are sick for other reasons.

We have documented that, both in Italy and in Spain, and probably the same has happened in our country, in the United States, places that saw these excess deaths had massive infections of medical personnel. In Italy, we have seen that as of one week ago that I had the latest scrutinized data, we had 14,000 people who were medical personnel who had been infected. In the US, it seems that in some locations, we also have very high rates, because, as I said, there is no vaccine for this coronavirus, much like there is for influenza. This means that the battle moves in the most unsuitable battleground. Hospitals are the worst place to fight the war COVID-19. We should have done our best to keep people away from the hospital if they had COVID-19 symptoms, unless they really had very severe symptoms, in which case, of course, they needed medical care. I think that in many of these places, unfortunately, we saw many people going to the hospital probably under a sense of fear and threat and panic, and we had the environment heavily contaminated, generating hospital chains of infection and therefore infecting lots of people who were very susceptible, and who would do very poorly if, on top of whatever they had, they also got COVID-19 infection.
We should be very careful. Coronavirus is not influenza. It's a different virus, it has a different propensity to spread, but it also has the ability to infect elderly and debilitated people, frail people, people who have underlying diseases, and the best location for the virus to find its victims is the hospitals, both acute care and chronic care facilities, and nursing homes. And this is really where we get massive infections and a very large number of deaths that goes beyond what we have seen in the large majority of locations around the world.
JK: But, in your recent study, I think there is a message to healthcare providers, in terms of the case fatality rate. Could you talk about that?
DI: A major concern about healthcare providers is that the early data that we had suggested that SARS-CoV-2 has a very high infection fatality rate. You remember the early quote by the WHO of 3.4% of people who get infected will die. You remember the estimates that were built in the early mathematical models by Imperial College, suggesting that 1% or .9% of people who get infected will die. And also, very high rates of hospitalization, even among those who do not die. You can imagine what that means to our heroes who are fighting on the front line in hospitals, physicians, nurses, and staff, thinking that if they get infected, they have 1 out of 30 chances of dying. Based on what we see now, it seems that the infection fatality is much, much lower. And, in fact, the data from Italy, which are the much more mature, suggest that the infection fatality rate is about .3 % for infected personnel. If you take into account the fact that Italy has the oldest, or one of the oldest, medical personnel workforces in the world, and if you also account for the fact that a very large number of personnel probably have not been tested, and must have been infected because we see that the majority of infections tend to be asymptomatic, or extremely mildly symptomatic, if you correct for these factors, you get to the same estimate that is very close to the infection fatality rate of influenza, also for medical personnel. This means that probably we can offer some reassuring message to these heroes who fight night and day under very dire circumstances. At least, we can tell them that their risk of dying is not what was thought to be the case.
We also need to give a very strong message that stringent infection control and hygienic measures within the hospital environment, both acute and chronic care facilities, is of paramount importance. Also, we need to give the message that patients who think they may have symptoms of COVID-19, they should not go to the hospital. That's not the place to go, really. Patients with other problems, serious problems, are avoiding going to the hospital, unfortunately, and these people should go to the hospital. But if someone has these mild or even moderate symptoms with COVID-19, they should not go to the hospital. I think we should also think about the need to detect infections in the hospital environment, so, for example, universal screening of medical personnel, and the use of quarantine for people who are detected to be positive, may also help to eliminate this infection that may be spreading in the hospital environment, especially in overcrowded and overwhelmed locations.
JK: Okay. Just moving quickly through some of the other studies that you have done. Another study you published earlier this month is called, "Population COVID-19 mortality risk for non-elderly

individuals overall, and for non-elderly individuals without underlying conditions in pandemic centers." What did you study in this case and what did you discover?
DI: This study was an effort to put together the evolving data sets from several countries and several states in the US, trying to understand how much bigger is the risk of people who are less than 65 years old, versus older individuals, and also try to get some estimates of their absolute risk of dying during the COVID-19 pandemic. We also tried to see whether people who also did not have any underlying conditions were likely to die. You have seen in the news multiple stories about young people with no health problems, who get severe outcomes and die, and many such cases are reverberating, and obviously creating a sense of horror and panic. We wanted to see how frequent that is, and how big is the exact risk of dying if you are at different age groups. The first major finding is that if you compare people who are less than 65 versus those who are above 65, there's a huge gradient of risk. The risk is about 70 times larger in those who are above 65, or equivalently, 70-fold lower in those who are less than 65, in 8 European countries that we analyzed. And the risk gradient is a bit smaller. It is about a 15-fold difference in the US, but still very large difference. You can imagine what it means to have 15 times lower or higher risk of death.
We also saw that the proportion of people who are less than 65, in terms of the overall pool of deaths, accounted for anywhere between 5-9% of all deaths in European countries, and a somewhat larger percentage, ranging from 20-30% in some states in the United States that have started accumulating some data, as the pandemic is maturing. We also tried to estimate, what is the absolute risk if you are less than 65, and we tried to compare that against the risk of dying if you drive your car over a given distance. In doing this, we tried to correct for the number of days that the pandemic is ongoing. So, you can get an estimate per day. In many locations, like Germany, the risk of dying from coronavirus until when we did the analysis on April 4, is in the range of the risk of dying driving from home to work or even less. In—
JK: If you're under 65.
DI: If you are 65 or less, indeed.
JK: With or without underlying conditions?
DI: With or without underlying conditions. In the US, where we have a larger share of people who are a bit younger, compared to the European countries, that risk is higher, but still it is not in the range that someone should really be afraid of dying. It is in the range of driving, you know, not from home to work; in the case of New York, of course, it's much higher, it's equivalent to the risk of a truck driver who has long shifts every day, driving for many, many hours, but still this is something that some people do for a living. So, I think that if you take that perspective, and acknowledging for the fact that the epidemic is still evolving, and we cannot be sure whether we will hit even higher peaks in the future, although this doesn't seem to be the case, at least for the European countries, and it seems to be that even in the US, in most states, we are very close to the peak, if not past the peak, the risk is something that should be manageable, as opposed to the panic and horror stories that are circulating about a risk that is amazing and completely beyond imagination to deal with.
JK: There was another aspect to the study we're discussing now, which is that people 65 or under without underlying conditions have what risk? It seems that you were saying it was negligible. Could you speak about that?
DI: People who are less than 65 and have no underlying conditions is extremely, extremely tiny. These people account for less than 1%, actually many countries in Europe, less than .5% of all deaths that we see, and in the US data that we have from New York suggests that they are a little bit over 1%, but not much so. So, for someone who is less than 65, and has no underlying diseases, the risk is completely negligible. I think that we have to see whether we get additional data and we have a more granular view of some people who still do not have an in-depth assessment of their medical records, but it seems that these deaths are extremely exceptional, but very unlikely.
JK: And in a place like New York, it's slightly higher. And you said that's because there's a younger population or, I'm sorry, why is the risk higher in New York?

DI: In New York, the risk is substantially higher, and this is why I use the analogy of a truck driver who is driving long shifts on a daily basis. We have to wait and see how the data from New York City matures, though, because they're really an outlier compared to any other place in the country, and even any other place in the world. We clearly have a very large number of deaths in New York City. There is some contentious issue about what exactly should count as a COVID-19 death. For example, in the last few days, we have seen a very large number of probable COVID-19 deaths being added to the figures. And these are deaths where we have not documented, with laboratory testing, the presence of the virus. So, they are pretty presumptive, in terms of whether these are deaths that were caused by COVID-19, COVID-19 was present but not really a key player in the demise of the patient, so, I think we need to wait and see some mature data on what, exactly, the contribution of the virus has been in different deaths that we have documented.

In Italy, where we have some more mature data, we see that close to 99% of people have underlying diseases. Actually, in most cases, multiple underlying diseases and underlying causes that could also have led them to death. In the US, it seems to be less, but we would need to get some more in-depth analysis of what, exactly, is killing these people, and how.

JK: I want to get back to the addition in New York city of 4,000 deaths, and the CDC guidance to assume COVID-19 in particular deaths, in many deaths, but if you could just outline for us, you published a piece in the *Journal of the American Medical Association* concerning Italy. Could you tell us what the gist of that was?

DI: So, the data in Italy suggests that it's very difficult to differentiate between deaths *by* SARS-CoV-2 and deaths *with* SARS-CoV-2. Since we had close to 99% of people dying have other causes that may have contributed to their demise, it's very difficult to dissociate and say that these people specifically died because they were infected. It's very likely that many of them would have died anyhow, if not immediately, within a very short period of time, because of these other causes of death that they had. I think that this is an ongoing debate, and I think that we will need to sort that out, not only for Italy, but for every other country. Countries use very different systems of recording deaths, and we know, not just from the COVID-19 era, but also from the past, that filling out death certificates can be very tricky. We know that death certificates often are pretty inaccurate, and if you create an environment where people believe that this is the cause of death that is really the most prominent at the moment, they may subconsciously, or unconsciously, prefer to list COVID-19 as a major cause of death on the certificate, even though it may be a less significant contributor, if not an innocent bystander, in some cases.

This is very difficult to tell at the moment, because, as you realize, the battle is still ongoing, but at some point, we need to go back and check very carefully, and try to understand, what exactly did the virus do to all these people? If we do that, we will be able, also, to estimate how many years of life were really lost. Because it's not just the number of deaths, but it's the number of person years lost that matters the most. If you have someone who is young and healthy and has no other problems and suddenly dies in their 20's, this is a very large number of person years lost, compared to someone who is very old and has multiple reasons to die, and is already dying from something else, and you just happen to find a PCR positive test for SARS-CoV-2 in a nasal swab. The number of person years lost is very small, and you're not even sure that SARS-CoV-2 really did contribute to their death substantially.

JK: Just, as an aside, now that you've mentioned the PCR test, we've seen, recently, that the inventor of the PCR test, who is now deceased, had said it should *never be used* for testing for infectious diseases. Are you aware that he said that, and what is your position on the PCR test as an accurate guide, since it, you know, seems to find such small pieces of genetic material, as opposed to an antibody test? You know, what are the distinctions there?

DI: I think that all tests have advantages and disadvantages. PCR was a major breakthrough for medical science. It did allow us to be able to detect different things, including infectious pathogens, if they were present, if their genome was present, in very, very small amounts. As you realize, that also creates a situation where you may be able to detect something that does not have clinical significance. It's very, very good at detecting things, but then you have to ask, "So, does it really

matter for what I'm seeing in terms of the clinical course?" In many cases, the picture is very clear cut: you have a clear syndrome of respiratory failure in someone who had no problem, and this thing has happened acutely, and then you get positive PCR, and you don't see a positive test for other viruses or for other causes. I think that this is a very clear picture. But, in many others, it becomes far more fragile as a diagnosis. I think PCR is a great tool, provided that we know what it means, and how it is interpreted. Another drawback is that what we detect is fragments of virus, not necessarily infective virus. So, it doesn’t mean that someone who has a positive PCR is also infectious at the same time. That's something that may not be the case.

Antibodies is a different story, and antibodies have been developed as a technique for even longer time, compared to PCR. We have had the ability to measure antibodies for many, many decades now. And, they give us an answer to a different question. They give us an answer to the question, "Do you have some evidence that you have mounted an immune response to the virus or to whatever else you might have been infected [with]?" Problems with antibodies include the fact that they need to be very carefully validated. So, you need to have some very good sense of how sensitive they are, meaning, how many people who have been infected they are able to detect antibodies in, and how specific they are, meaning is it possible that someone may have a false positive test and you believe that they have antibodies but actually, they do not. And there are many reasons why that may happen; if the antibody test is not very carefully designed, it may pick some cross-reactivity with some other viruses, for example, some old coronaviruses that were circulating in the past.

This is why both PCR and even more antibody tests need to be very carefully validated. We need to check them against samples that we know for sure that correspond to people who have been infected, and we need to test them, also, very carefully, against samples that we know for sure that they do not have SARS-CoV-2. For example, they are samples that were collected 2 or 3 years ago, and therefore, SARS-CoV-2 would not have been around at that time. This is pretty much what we did in our study. We very carefully validated the antibody tests that we used, and I think that other antibody tests are also being validated pretty thoroughly. You need to take into account their performance, what we call their “sensitivity and specificity,” in generating reliable estimates about what the results mean.

JK: What do you think about what is currently being postulated, that it's possible that those with the antibodies may not be immune in future? What is your sense of that?

DI: I think this is very speculative, and obviously, it's a hypothesis that we need to pursue. There's two possibilities, actually, that lead to different conclusions. One, is that you have antibodies, but these would not be enough to protect you from future infection. I think this is not very likely, although it becomes likely if we are talking about protecting you from infection, let's say next year, or 2 years or 3 years down the road, because it is possible this coronavirus will change itself, if it ever comes back. We just don't know when and if it comes back. It may be a different variant, and much like we see with other viruses, and much like we see, even with influenza, and this is the reason why, each year, we try to prepare a new vaccine to cover the new types, it is possible that the antibodies that we develop now would not be able to cover this new variant. Or that the titers, the levels of the antibodies, will go down after a given time; unlikely that they would go down very quickly, but if we're talking about a year or two years from now, who knows? It could be that they are no longer in sufficiently high titers.

JK: When one has the measles, the wild measles, naturally, one is given lifetime immunity. And yet, when one gets the measles vaccine, one can become reinfected with the measles within 10 years or perhaps even less. Does that speak to whether or not we should be trying to immunize in a different way from SARS-CoV-2 than with vaccination?

DI: It's pretty early to say, but I would like to give you, also, an opposite perspective. So, we talked about the possibility that, even though you have antibodies, you're not protected. Which, I think, it's not likely, although in a time horizon, it may become likely. There's the alternative possibility that you do not have detectible antibodies, but nevertheless, you have encountered the virus, and you have generated some immune response, and somehow you have cleared the virus, and you're okay.

And there is some preliminary data that suggests that, particularly in young individuals, many of them, perhaps in some cases, the majority, they do not develop, necessarily, high enough antibody titers, but nevertheless, they clear the virus, and they have full recovery with absolutely no problem. What that might mean is that our ability to deal with SARS-CoV-2 may not necessarily depend just on antibodies.

Our immune system is very complex. There's many mechanisms of innate immunity, and perhaps, there's other ways that we can still handle a virus and not be at risk any longer. This is still something that we need to explore in more depth. We need to find out what exactly we need to be protected. Depending on what the answer is, the prospects of a vaccine may be more favorable or less favorable. For example, the classic vaccine typically wants to generate an antibody response and make sure that response would last. As you realize, if there's other mechanisms that are equally good or better, then this becomes less relevant, and also, if that antibody response only lasts for a short while after vaccination, then again, a vaccine that aims to do that becomes less relevant.

JK: I'm very interested to hear you say that, because of course, on the one hand, we have for instance, the Bill Gates Foundation, which is suggesting that they are going to produce 7 billion doses of vaccine for SARS-CoV-2. And some within the WHO, CDC, and the Gates Foundation, seem to be suggesting that we won't make it out of - that we oughtn't get out and into our normal lives, until there is a vaccine. So, you're saying the jury is out on that?

DI: I would like to be optimistic, that we should be able to regain much of our functional life before a vaccine becomes available, if ever a vaccine becomes available, because, as we discussed, there's all these caveats about the ability to get a vaccine done and get it out there in massive production. I'm a great fan of vaccines. Throughout my career, I have tried to kind of disseminate the message that vaccines are one of the greatest contributions of science to humans, and they are great success stories. We have several vaccines that are wonderful success stories. This doesn't mean that necessarily we will have a success story with a vaccine for coronavirus. We have some experience from the past from efforts to develop vaccines for the other coronaviruses that we were aware [of], and they were not very successful. One concerning observation is that in some cases, vaccines were developed for animal models of coronaviruses, because we have coronaviruses that infect cats and other animals, and they caused more damage than not giving them at all. Because they led to a hypersensitivity response. So, when the animal was exposed to the coronavirus, it overreacted to the virus. And that actually could even lead to death and worse outcomes compared to not having been vaccinated at all.

We need to understand what is the exact mechanism that is leading to severe outcomes in humans and death, and we need to understand whether it is the virus itself or the immune response to the virus that is doing more damage in different cases. If it's the virus, and what the problem is, is that we don't get enough of an immune response, then we need to have a vaccine. If the problem is that it's the overreaction of our immune system that eventually leads, accidentally, to destroying our own cells, like lung cells, then a vaccine may actually be a bad idea. Bottom line, a vaccine needs to be very thoroughly vetted, very thoroughly tested. We need to have solid evidence that it works, solid evidence that it makes things better, solid evidence that it will save lives. And this cannot be done overnight. I wish that we could do it very fast, and I want to see these studies done, and I know that lots of brilliant scientists are working on this front, and I want to remain optimistic, but it's unlikely that we will be able to wait for 12 or 18 or 24 months to get a vaccine and even more so under such uncertainty.

I don't think that we can remain in lockdown states for so long and not just destroy ourselves, destroy our communities, destroy our societies, create huge problems for health, for unemployment, for our economy, for our society, that are much worse than even the worst and most pessimistic scenarios of what coronavirus can do.

JK: I want to get back to that, but, just very briefly, have you happened to run into a government study that showed that people who had the flu shot were more susceptible to non-influenza pathogens?

DI: There are some data that are coming out about this issue. And I think we need to wait to have some more mature data sets across multiple countries and try to understand what that means. We have seen that in some locations. For example, in Italy, we saw that, in the three months preceding the outbreak of COVID-19, with these massive deaths being documented, these three months had been particularly good for the Italian population, in terms of deaths, in particular, deaths from influenza and related pathogens. In a way, though, that would mean that there was a surplus of susceptible individuals that typically every winter would perish because of influenza, and these people didn't perish this winter, and that pool of susceptible individuals was then available for coronavirus to attack very fiercely and kill many of them, is that evidence that somehow there's some antagonism between influenza and coronavirus for occupying the same niche? I think that this is something that we need to look into, but it is a definite possibility, that somehow these viruses are competing for the same pool of susceptible individuals, so if you save people from one of them, they may still succumb to the other.

JK: Just in terms of the general numbers right now in the United States, what is your sense of - I think the CDC may have said there were 60,000 influenza deaths, we're obviously well below that, in terms of COVID deaths. Would we, as you earlier suggested, if there weren't a certain amount of attention paid, would we have noted the addition of the corona fatalities to the normal flu season? What's your sense of the relationship between these two things?

DI: I think that, based on what we see now, clearly that would have been a detectible wave. It's a wave that in most places around the world, including in the United States, it's fairly acute, so we do see a clustering and an accumulation of both symptomatic disease and death. So, it would have been detectible as something that is beyond what is the typical baseline for this particular month, for March and for April. In terms of how big that wave is, in terms of total deaths, that's a bit early to give an exact number, but clearly, I think, we have avoided all of the apocalyptic scenarios that were circulated early on, about 40 and 50 million people dying around the globe, and 2.5 million people dying in the US. As we speak now, we have over 30,000 deaths being recorded, but as you realize, these also include these probable cases, and, as we discussed, one needs to return and see, at some point, how many of those really were caused by COVID-19. So, it is a serious problem. No one would deny that. But it's clearly not the apocalyptic problem that we thought we would face early on.

We have data now that the infection fatality rate is much, much lower, compared to our original expectations and fears. I think that there is no reason to fear. We have data. We have ongoing accumulation of data. We have eyes on the epidemic and its evolution. We can be - we should avoid panic, and we can take rational steps to deal with the situation, and then hopefully, even open up our society again with careful, gradual steps.

JK: Okay. I have got to ask, what do you think accounts for the huge discrepancy between the initial projections and what we're seeing now? I think, in particular, of the Imperial Study from Neil Ferguson, where 500,000 deaths were forecast in the UK, right after the Oxford study came out that took issue with that, he changed his forecast to 20,000 or under, but said that this was due to 1 days' worth of - there'd been 1 days' worth of social distancing, he said this was due to the social distancing measures. What do you make of that claim and what do you make, in general, of the huge variation between the initial forecast and what we're actually seeing?

DI: The problem with the Imperial College study, and other similar studies that try to forecast the number of deaths early on, is that they used a very inaccurate inputs in their modeling. You know, the scientists who did these calculations, they're knowledgeable scientists, but even the best scientists in the world, if you give them estimates of perimeters that are completely off - in this case, actually astronomically off, compared to reality - they will get astronomically wrong results, and I think that this is what happened. And I am not saying this to blame anyone - it's amazing that they could put their work together so quickly. But, the input that led to their calculations was completely wrong, based on what we see now. In their subsequent efforts, they tried to decrease some of these estimates to more meaningful numbers. And then the question becomes whether these

massive decreases, versus the original estimates, are due to measures, or due to correction of some of these wrong estimates that were used as input in the beginning.

Clearly, wrong inputs is a very big component, because they had to change, for example, the infection fatality rate that went into the calculations, and this, immediately, dramatically, decreases the number of estimated deaths. How big is the contribution of social distancing measures? I think that this remains an open question, and we need to accumulate the full picture of what happened in different countries before we can tell what exactly social distancing did for us. And even more so, what different aspects of social distancing achieved. Within the bag of social distancing, there is a very large number of different measures. Like, for example, school closures, or closing shops, or avoiding mass gatherings, or avoiding travel, or avoiding people getting together and if so, what is the threshold of avoidance? Do you set it at not allowing more than 2 people to get together? More than 3 people? More than 50 people? Or what? Each one of these measures, I think, could have different connotations and could have different effectiveness in the field. I think that just saying that the measures worked is a very, very poor statement. it's an over-generalization, and I think that we need to scrutinize very carefully which one of these measures worked, which ones did not work, and which, actually, may have done some harm.

In principle, I think that we should not blame anyone for just acting ferociously and aggressively and saying, "Shelter in place immediately. We just don't know what's going on." It was a very sound approach. But now, we can be a bit more thorough, a bit more exact. For example, school closures: the evidence that we have suggests that maybe school closures decreased deaths by about 1/50th, like 2%, in relative terms, which is a very small number. Again, this is preliminary knowledge, and it needs to be vetted and examined in more depth, but if really the benefit from school closures, especially kindergarten and elementary school, and even middle school, is so tiny, and the consequences, the adverse consequences from closing schools are far bigger, in terms of many other consequences that could also translate down the road to death equivalents - if you destroy society and the economy - you are likely to pay that in deaths among citizens.

JK: And, isn't there also a component to closing the schools that, in terms of the virus, could have been counter-productive? Isn't the concept behind group immunity getting an airborne respiratory virus to spread among those who have, really, no problem with it, so that, therefore, you've built that group immunity, and you can shelter the vulnerable while the rest of us deal with the virus and it then has no more hosts to go through, and you can dramatically decrease the amount of time that older people have to shelter?

DI: This is clearly a possibility. And we need to see the full picture before we can pass verdict on it. But, indeed, it is possible that since little kids and children in general don't really get severe diseases - most of them are entirely asymptomatic, or mildly symptomatic - they could contribute towards a pool of herd immunity without getting into trouble themselves. And if you could protect elderly and frail individuals from being exposed to kids, maybe you would have done better, compared to closing schools and asking kids to live in close quarters with their grandparents, and with frail relatives and then infect them. It's also an issue of timing. For example, different lockdown measures may have different benefits and different harms, depending on what stage of the infectivity, or the epidemic wave, they're applied at. I think they may have different ability to limit the number of infections, or actually increase the number of infections, depending on whether they are applied in an early stage or a late stage.

If you go into lockdown in a situation where the virus is already widely circulating in the community, and 30% of the people are actively infected, and you tell them, "Just go and stay at home, with your relatives, with your grandparents, with your relatives that have severe diseases," then you're forcing these people to just stay in close quarters day and night with these vulnerable individuals. Well, this doesn't seem like a very good idea. It varies, also, from one place to another. The ability to shelter in place is very different for me. I have a nice house and I have all the space I need. I can be far apart from my daughter, if I wish to. But, in most places around the world, most people cannot really shelter in place effectively. Many of them have to go out to work, because they work in essential types of work that we all depend on. Many others have no place to shelter at all.

We have a very large population of homeless. They might go to a shelter, and we have seen, recently, data that suggests that this is the worst place to shelter, because 35% of homeless people in a shelter in Boston tested positive for coronavirus. So, in a way, we forced them to be infected, which is completely horrible. We are making things worse for them. Instead of trying to help people who are disadvantaged, we are making them even more disadvantaged and even more unequal with many of the measures that we are taking that are protecting some of us that are better off, but are leaving large segments of the population, both in this country and even more in other countries - you can think of the third world - completely unprotected.
JK: Now, but, in the case of that homeless shelter, weren't most of those, or all of them, actually asymptomatic in the end?
DI: So far, none of them had symptoms. Of course, we need to watch and see whether any of those might develop symptoms, but as you realize, we know very well that the chances of developing symptoms are much higher in people who are older, and in people who have underlying severe diseases. So, young homeless people maybe are infected, and they just don't realize that, and they do well. But there's a lot of people out there, who are homeless, who are disadvantaged, who really have a rough time. And if we get to get them infected by what we do, that would be a disaster. I think that, I really worry, also, that with many of the measures that we are taking, we might be creating armies of unemployed people without health insurance. We may be creating more homeless people. We may be creating people who are disadvantaged, and in the setting of a pandemic, they will become easy victims while we are sitting in our nice houses.
JK: Doctor, I know you are diplomatic to a fault and very kind to your colleagues, but people have been asking me to ask you, how could very smart people at the WHO, Imperial College, etc, make such an excessive mistake? It just seems...this order of magnitudes mistake, is there any possibility that it's not just a dumb mistake? I mean, could they have just been that truly, deeply, profoundly wrong? With such horrible consequences?
DI: Unfortunately, yes. And I think that we should not see that as evidence that science is failing, or that even these scientists have failed. These scientists who created these models, they work under extremely stressful conditions with extremely limited evidence and when you have stressful conditions and very limited evidence, the default option is to assume the worst, and try to protect people from the worst. So, I think that this is what they did. I don't think that we should say that they were bad scientists. They got it astronomically wrong. I think that that's indeed the case, but science got it right eventually, and it got it right pretty quickly, I would say, under the circumstances, and under such a situation of panic and chaos. So, I think that we should remain cognizant of the power of science, of self-correcting itself, of getting things to be correct, eventually, and hopefully pretty soon, and really being the best thing that have happened to human kind. I think that science is the best thing that we have as humans to guide us. We just need better and more accurate science.
JK: I'm a believer, I'm with you, doctor. But, here's the thing: you have been a corrective force, and many other epidemiologists and doctors, but to this day, the Trump Administration, and I won't make a distinction between the Trump Administration and Fauci, and Dr. Burkes, they are suggesting that, as is Neil Ferguson, that if we had not social distanced, we would in fact, have seen 2 million deaths. Does your - In the United States - does your work suggest that the case-fatality ratio, with or without social distancing, would mean that that was not the case? Is that what your serology study in California teaches us?
DI: Both our serology study in California, and several other studies that have started releasing some information about rates of infected people that are also very high in different locations around the world, suggest that the infection-fatality rate is very, very low. So, these scenarios of 40 million deaths in the world, and 2+ million deaths in the US, by doing nothing, are science fiction at the moment. I cannot describe them in any other terms. This does not mean that social distancing did not have any benefit. I think that we have to be very cautious, and we have to revisit each one of the components of social distancing, to see which one of these components work, and perhaps, which of these components actually created some harm. We just need to remain calm. It's not time to blame

each other. It's not time to say, "I was right, you were wrong." I'm sure that I make mistakes day and night. I'm a scientist. I make mistakes, and I'm just trying to correct them. I'm just trying to get better data. And next time we speak, if I have better data, and this suggests that I was wrong in any of my statements, I'd be very happy to acknowledge that. We just, to be open, we need to be transparent. We need to trust science, and we need to move forward and reopen our world carefully, cautiously, but in a data-driven mode.
JK: Now, "carefully, and cautiously." Does that mean of necessity, contact tracing? Is contact tracing even a scientifically feasible idea in a city like New York, where if I travel through Times Square or Grand Central Station, I am in contact with hundreds of thousands of people on a daily basis, and more, if indeed, this virus lives on surfaces for 3 days. So, this...but...this is the drumbeat, that we will have to have this. Is this a scientifically feasible notion in the first place for an airborne respiratory infection?
DI: Contact tracing makes sense in a situation where you have a very limited spread of the virus, and you have very few people who have been infected. You know what is the index case, and you can track 10, 20, 30, 40 people who have been exposed, and then identify those who are infected, quarantine everyone, and try to extinguish the epidemic. In some sense, it has worked fairly well in countries like Taiwan, Singapore, South Korea, where they were very aggressive in testing and identifying people who were infected, and then trying to identify also their contacts. But it's not something that you can easily apply in the vast majority of locations. And clearly, it's not easy to do in a country like the US. You have to realize that one size does not fit all. And I have always been in favor of more testing. Because it gives us better insights into the epidemic. I have been in favor of random representative testing as well, because it tells us with more accuracy, what is the stage of the current infection wave, how many people have been infected, and or how many people are actively infected. But for locations where you have 10%, perhaps 20% of the population already infected, contact tracing, you can imagine, almost everyone in that location has been exposed. So, New York City, for example, at the moment, we are in the process of launching a seroprevalent study, hopefully very soon. If, say, we get an infection rate of 30% (30% of New Yorkers have been infected), it's very likely that almost every other New Yorker has also been exposed to them.
JK: You're saying, I'm sorry, could you say that again? If 30% of New Yorkers have been infected-
DI: This is entirely speculative, as you understand, but if 30% of New Yorkers have been infected, then the other 70% must have met almost all of them, some of that 30%, pretty recently. Therefore, contact tracing means just the entire population, in that case. And even with lower percentages, that 30% was entirely speculative, and please don't say that I came out and was prescient about anything, but even if you have 5% of the population being infected, again, 1 out of 20 people, each one of us is meeting lots of others in our daily life. Even under conditions of shelter in place, I mean, many people have to work. Many people go out to shop. it's going to be very difficult, if not impossible, to really track down everyone that that 5% has exposed.
JK: Please describe the strategy chosen by Sweden and what is it telling us now?
DI: Sweden was one of the countries that chose a less-restrictive approach. It kept much of its society and its economy open. It allowed most schools, kindergarten and elementary school, and middle school to be open. It kept most shops open, and bars and restaurants, although with some modest restrictions. It also allowed people to get together, but not exceed a limit of 50 people. So, in a way, it is very different compared to the draconian measures that were implemented with very fierce lockdown measures in other countries in Europe and in many places in the US. They have done fairly well. And, of course, it is very difficult to compare one country against another, because you expect to see large diversity in infection rates and also in death rates. A country like Norway for example, where the average Norwegian is likely to see very few other people, you know, it's very sparsely populated compared to Stockholm, is not something that you can compare head to head. Maybe you can compare Sweden against Switzerland, for example, that had very draconian measures very early on.

And the death rate per million population is slightly higher, a bit higher, in Switzerland, compared to Sweden, until now. These are very, very tricky comparisons. These are comparisons that need to be made with great caution because they are observational data. You cannot create a Sweden in Switzerland. You cannot create a Switzerland in Sweden. So, all of these claims that you will see circulating, that "This is definitive proof that the lockdown worked," or even conversely, that "You didn't need that at all," I think that we have to be very cautious. No evidence so far though, suggests that Sweden did something wrong, I think that they seem to have fared pretty well. They had a number of deaths. The number of person years lost was pretty small because almost all of these deaths were in people who were very frail and old and had very limited life expectancy. They never came close to seeing their health system crash. They always had plenty of reserves. At least until now. That might change in the future, and I am watching that very carefully. But, I don't think that we can blame the Swedes for doing what they did. Maybe we should congratulate them.
JK: And what do you think of the German health minister suggesting that they open up nursery schools right away?
DI: I think that this is an interesting suggestion, and both Germany and other countries in Europe, like Denmark, Austria, and even Italy, are taking steps at the moment, as we speak, to open up different segments of their society and of their economy. I think we need to see what happens. And I am in favor of such steps, if you have a situation where you have peaked infections and you start declining, you have eyes on the epidemic, you know that it's not out of control, if you know that your health system still has a lot of capacity, that no matter what happens, you still have a lot of reserves of beds and ICU beds. And all of these countries, Germany, Denmark, Austria, have plenty of reserves at the moment. Even Italy is taking steps in opening shops and some businesses, and in these areas that this is happening, they have the ability to track what happens and what might be the evolution of the epidemic, as they do that.
I want to remain optimistic, and I think that more countries should take these steps, if they have these prerequisites in place, and see what happens. I don't think that we will be killing people. We need to do that and see what happens, because otherwise, we will be killing, massively, people because of the lockdown measures.
JK: So, speaking of the lockdown measures, was - and I'm just going to give you all three of these at once, and you can opine on them as best you can, and especially in light of Sweden, I'm very curious - was social distancing helpful in flattening the curve? Then, was flattening the curve helpful for reducing stress on hospitals? And does flattening the curve ultimately result in fewer deaths or in just spreading them out? Do we, inevitably, have to follow the susceptible infectious resistant curve, the epidemiological curve, no matter what, and all we are doing is pushing it down stream? That seems to be the suggestion. And then, I guess, really, since we've never, ever done this before, I guess you have to speak to the value of social distancing, as best as we can ascertain it now, but did the concept of flattening the curve actually help, first of all?
DI: So, if you look at what the proponents of flattening the curve theory have suggested, which is a very interesting theory, and may well be correct, is that you do that not to save lives, but to postpone the epidemic wave, in a sense to flatten the curve, and allow you to gain time to be better prepared. For example, get more beds in place, get more ventilators, prepare your hospital for that major battle to be fought, prepare your testing capacity, get enough protective gear - you're buying time. But, eventually, sooner or later, once you decide to remove the shelter in place situation, you are back to a virus that needs to spread, and it will spread, and it will infect the people that it didn't infect immediately, but it will infect them later, and you're just better prepared and with better capacity to deal with that. There is an excess of death load if the healthcare system crashes. I think that we have seen that, because in that case, you cannot really offer care to people and some people who might have been saved, if they had a ventilator available, they are dying because this is not an option.
However, with much of that shelter in place approach that we have followed, we have seen collateral damage on health, in that many people who have other serious conditions like heart attacks, or strokes, or things that they desperately need to go to the hospital [for], they don't go to

the hospital, because they have been in panic, they fear, they see all the news stories about how horrible this thing is, and they just don't want to go anywhere near the hospital. We know that for these common things that caused a large majority of deaths, modern medicine is effective. It can save lives.

And if these people stay at home because they are overdoing that shelter in place, and overinterpreting it, we may be killing more people than any that might be saved by any measures for coronavirus. So, we have to be very careful. I think that it's very unfortunate that we had such astronomically wrong numbers early on. Unavoidably, based on these numbers, we had to sound the alarm. Unfortunately, people did panic. They did fear. Unfortunately, our hospitals, now, in terms of the non-COVID-19 wards, most of them, many of them, are empty or completely underused, compared to what has been the typical utilization. And I think that this may be a huge problem.

JK: Now, your study, and this is the headline for me, your study, and I know you need to replicate this, I know it needs to be peer-reviewed, I know it's early days, but your study has essentially shown that this thing is as, the case fatality rate is the same as, seasonal flu. So, shouldn't the major recommendation now be to open up as soon as possible. Maybe keep sheltering the vulnerable, but should we not be shouting from the rooftops that it is time to open up?

DI: I think that it is time to open up in many locations, and the time is coming for others. I think that if we are careful in collecting information on how the epidemic is evolving, to make sure, and to offer confidence and self-confidence to all people in our community that we haven't lost control of the epidemic - because many people will still be very fearful, they will say, "I don't want to go out. I don't want to do anything. People are still dying!" - if we do that, if we offer science, if we offer reliable data, if we offer reassurance that this thing is not going to kill you, it doesn't seem to have a higher chance of killing you than, you know, seasonal flu, for each person who is infected - although we know that there are some people who have a much higher risk, and these, of course, we need to protect, very, very, carefully - I think if we put that agenda in place, we could open up. And I think it needs to be gradual, it needs to be reinvigorating confidence in the population that the right thing is being done, and it is to the benefit of our society and our citizens, and all people. And then, I think we will do well. We will have to watch it very closely, but if we don't do that, I don't really see an alternative.

JK: You said, in your previous interview, you're just a simple scientist, which I appreciate, and not political. I just, I want to get you to reiterate this in some way. Because we see that the battle over opening up or remaining in place seems to be falling along partisan lines, not just in the United States, but all over the world, as if there is, you know, almost a battle either between left and right, or between the bureaucracy at the CDC and the president, or what have you. Are you above this fray? Are you a Trump supporter or an anti-Trump supporter? Is- are you politically motivated in some way? Do you prefer the economics of the world over the lives of people? Anything like that?

DI: I have to reiterate that I'm just a simple scientist who is just trying to correct one's own mistakes. I'm just trying to correct my mistakes and get it right, and save lives. I have absolutely no political agenda behind my thinking and my calculations. Calculations and science are the same, regardless of what political party one belongs to. They should be the same. And I think it is a major shame to really turn this into a political battle. There's lives at stake. There's lives of our fellow citizens. There's lives of people who are disadvantaged. There's lives of our relatives, there's lives of everyone. They are at stake. And I think that it's horrible to turn that into a political battle, either in this country or in any other country. We should remain united. We are *homo sapien sapiens*. Humans the wise. That's what we should be. Not just partisan people who want to elect one president or another or promote the agenda of one political party. We are *homo sapien sapiens*.